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LETTER TO THE EDITOR

Treatment of Severe Refractory Acute Graft-versus-Host Disease of the Gastrointestinal Tract with Campath-1H

There is no consistently effective therapy for patients with steroid-refractory acute graft-versus-host disease (GVHD). A variety of alternative approaches have been tested, including antithymocyte globulin, mycophenolate mofetil, pentostatin, and monoclonal antibodies; however, these treatments have been only modestly successful [1]. GVHD can occur when transplanted donor T cells recognize major or minor histocompatibility complex proteins and their associated peptides presented by recipient antigen-presenting cells, such as dendritic cells. Campath-1H is a humanized monoclonal antibody with specificity for the CD52 antigen, which is highly expressed on normal lymphocytes, as well as on monocytes, macrophages, eosinophils, and dendritic cells. On the basis of these observations, Campath-1H has been used extensively for GVHD prophylaxis [2], but few studies have investigated its efficacy for the treatment of established acute GVHD [3,4]. Here we report the case of a patient who had severe acute GVHD of the gastrointestinal (GI) tract that was refractory to multiple immunosuppressive therapies and who was successfully treated with Campath-1H.

CASE REPORT

A 41-year-old man presented with myelodysplastic syndrome (refractory anemia with excess blasts; International Prognostic Scoring System score was intermediate 2) in May 2004. The patient did not receive any chemotherapeutic treatment and received a hematopoietic stem cell transplant from his HLA-identical sister in July 2004. The myeloablative preparative regimen consisted of thiotepa 15 mg/kg and cyclophosphamide 120 mg/kg. Lenograstim-mobilized peripheral blood stem cells (7.8×10^6 $CD34^+$ cells per kilogram) were infused on day 0. GVHD prophylaxis consisted of cyclosporine 2 mg/kg/d intravenously from day −7 and methotrexate 15 mg/m^2 on day +1 followed by 10 mg/m^2 on days +3, +6, and +11. The patient had prompt hematologic reconstitution, with an absolute neutrophil count of 0.5×10^9/L on day +15 after transplantation. Bone marrow aspirate on day +33 showed normal trilineage hematopoietic maturation, and full donor chimerism was confirmed by fluorescence in situ hybridization analysis (97.9% XX). On day +43, the patient was readmitted because of deterioration of general condition, GI discomfort with persistent diarrhea, and significant weight loss. During the first week of hospitalization, he had watery diarrhea, with a stool volume ranging from 400 to 800 mL/d, and 2 episodes of severe bloody diarrhea that necessitated red blood cell infusions. Stool culture was negative for bacterial and fungal infections, and the patient was started on methylprednisolone 2 mg/kg/d for 2 weeks while cyclosporine was switched from oral to intravenous administration and parenteral nutrition was initiated.

The patient did not to respond to the initial treatment, and 17 days later, cyclosporine was replaced with tacrolimus while steroids were weaned. During the next 3 weeks, secretory diarrhea and GI symptoms worsened, and the patient was treated with etanercept 25 mg twice a week for 4 weeks with any remarkable improvement. On day +92 after transplantation, he underwent endoscopic biopsy, which confirmed the presence of active GVHD and excluded intestinal tract infections, including cytomegalovirus. Seven days later, the patient complained of severe crampy abdominal pain with intestinal distension and biliary emesis. Clinical and radiologic findings were consistent with the diagnosis of ileus, leading to grade IV acute GVHD, but no signs of cutaneous or hepatic GVHD were observed. A nasogastric tube was used to resolve the abdominal distension, although profuse diarrhea started again 24 hours later. Mycophenolate mofetil (2 g intravenously for 16 days) and sirolimus were added to tacrolimus without any remarkable improvement, and steroids were discontinued on day +106 (the total duration of treatment was 64 days). On day +108, he was started on Campath-1H; the treatment schedule included 1 mg of Campath-1H intravenously on day 1, 3 mg intravenously on day 2, and then the target dose of 10 mg intravenously for 5 consecutive days. Campath-1H administration was well tolerated, without major side effects. Mycophe-

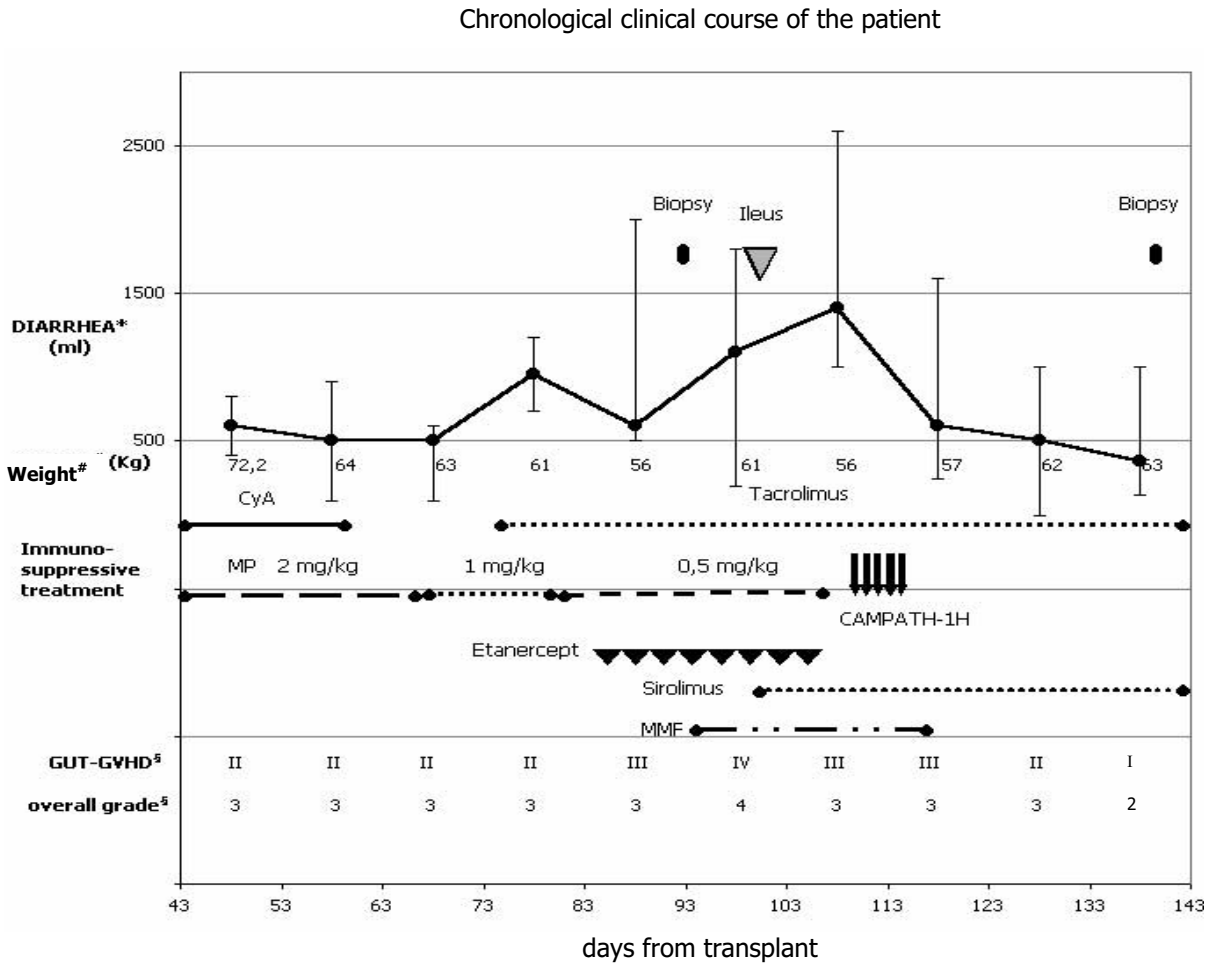

Figure 1. Acute gastrointestinal GVHD before and after Campath-1H. The response of intestinal GVHD to Campath-1H is denoted by remarkable improvement in stool volume after Campath-1H administration. *Median stool volume during 10 days; #median weight during 10 days; §maximum grade of GVHD.

nolate mofetil was discontinued after the last dose of Campath-1H, and the patient was maintained on tacrolimus and sirolimus. The stool volume begun to decrease to <500 mL/d as early as 3 days after the last dose of Campath-1H; over the ensuing 2 weeks, the median stool volume was 490 mL/d (range, 220-1620 mL/d), and he was able to initiate enteral nutrition. His general condition improved, as demonstrated by significant weight gain (from 56 kg before Campath-1H administration to 62 kg afterward). Histopathologic improvement was documented by endoscopy on day +142: erosions and apoptotic bodies of villi detected at the time of the first biopsy completely disappeared, but a modest decrease of crypts was still present.

The clinical outcome of acute GI GVHD is depicted in Figure 1. No bacterial or viral infectious complications were observed after the administration of Campath-1H. The lymphocyte profiles evaluated after the administration of Campath-1H showed that $CD4^+$ and $CD8^+$ cells were undetectable 15 and 40 days after the end of treatment, whereas the value of $CD16/CD56^+$ cells was within the normal range 40 days after Campath-1H therapy (157/μL). The percentage of $CD4^+CD52^+$ cells was 1.5%, whereas $CD8^+CD52^+$ cells were undetectable 40 days after Campath-1H therapy. On day +260, the patient developed chronic GVHD with cutaneous and hepatic involvement, which improved after treatment with steroids. At the time of this report, 10 months after the transplantation, the patient was able to eat normally and had limited chronic GVHD of the skin. He was maintained on tacrolimus (4 mg/d), and the dose of prednisone was gradually tapered from 65 to 30 mg daily.

DISCUSSION

Murine studies have shown that host dendritic cells that linger after transplantation may play a crucial role in the pathogenesis of acute GVHD [5]. In the light of these observations, the clinical response observed in our case suggests that host antigen-presenting cells may be a suitable target for GVHD treatment. Even though the data we presented are

restricted to only 1 patient, our observations reinforce what previous studies have shown: namely, Campath-1H seems to have significant activity in the treatment of refractory acute GVHD and should be considered for further controlled clinical trials.

REFERENCES

1. Antin JH, Chen AR, Couriel DR, Ho VT, Nash RA, Weisdorf D. Novel approaches to the therapy of steroid-resistant acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2004;10: 655-668.
2. Kottaridis PD, Milligan DW, Chopra R, et al. In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation. *Blood.* 2000;96: 2419-2425.
3. Carella AM, Beltrami G, Scalzulli PR, Carella AM, Jr, Corsetti MT. Alemtuzumab can successfully treat steroid-refractory acute graft-versus-host disease (aGVHD). *Bone Marrow Transplant.* 2004;33:131-132.
4. Wandroo F, Auguston B, Cook M, Craddock C, Mahendra P. Successful use of Campath-1H in the treatment of steroid refractory liver GvHD. *Bone Marrow Transplant.* 2004;34:285-287.
5. Sclomchik WD, Couzens MS, Tang CB, et al. Prevention of graft versus host disease by inactivation of host antigen-presenting cells. *Science.* 1999;285:412-415.

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